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Published in:
Journal of the American College of Cardiology

DOI:
10.1016/j.jacc.2016.01.015

Publication date:
2016

JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
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PUBLISHED BY ELSEVIER

VOL. 67, NO. 11, 2016
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2016.01.015

Acute Vasodilator Response in Pediatric Pulmonary Arterial Hypertension

Current Clinical Practice From the TOPP Registry

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ABSTRACT

BACKGROUND In pulmonary arterial hypertension (PAH), acute vasodilator response testing (AVT) is considered important to identify adult patients with favorable prognosis using calcium-channel blocker (CCB) therapy. However, in pediatric PAH, criteria used to identify acute responders and CCB use are insufficiently studied.

OBJECTIVES This study sought to describe current clinical practice of AVT and subsequent treatment decisions in pediatric PAH.

METHODS From January 2008 to May 2013, 529 consecutive children with confirmed pulmonary hypertension were enrolled in an international registry. We analyzed those children with evaluable AVT.

RESULTS Of 382 children with evaluable AVT, 212 had idiopathic/familial PAH (IPAH/FPAH) and 105 had PAH associated with congenital heart disease (PAH-CHD). In 70% of the patients, AVT was performed using inhaled nitric oxide; other agents were used in the remaining patients. In IPAH/FPAH patients, 78 (37%) patients were acute responders according to their physician, 62 (30%) according to REVEAL (Registry-to-Evaluate-Early-And-Long-term PAH disease management)-pediatric criteria, and 32 (15%) according to Sitbon criteria. For PAH-CHD patients, the numbers of AVT responders were 38 (36%), 14 (13%), and 7 (7%) respectively. Correlation between AVT responder status as judged by the treating physician and by published response criteria was poor. Moreover, of the IPAH/FPAH patients judged by the treating physician as acute responders, only 23% were treated with CCB without additional PAH-targeted therapy. The Sitbon criteria selected patients with better prognosis who had excellent outcome when treated with CCB.

CONCLUSIONS The current practice of identifying responders to AVT and subsequent treatment with CCB therapy demonstrated large discrepancies with current international guidelines. Also, in pediatric IPAH, the Sitbon criteria are the criteria of choice to identify patients with excellent survival when treated with CCB therapy. (J Am Coll Cardiol 2016;67:1312–23) © 2016 by the American College of Cardiology Foundation.

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The TOPP (Tracking-Outcomes-and-Practice-in-Pediatric-Pulmonary-Hypertension) registry is supported by an unrestricted research grant from Actelion Pharmaceuticals Ltd. Actelion does not participate in the management of the TOPP registry; neither does it have access to the database and the individual site and patient data. All decisions related to the Registry lie solely with the Executive Board of the Association for Pediatric Pulmonary Hypertension. The M3C-Necker contracts with Actelion, Bayer, and Lilly for Dr. Bonnet to perform consultant activities and to participate in steering committees for clinical trials. Dr. Beghetti has received grants from and contracted as consultant for Actelion and Bayer-Schering; and served as a consultant and participated in the steering committee for Actelion, Bayer-Schering, GlaxoSmithKline, Eli Lilly, and Pfizer. The University of Colorado contracts with Actelion, Bayer, Gilead, Lilly, and United Therapeutics for Dr. Ivy to be a consultant. The University Medical Center Groningen contracts with Actelion, GlaxoSmithKline, Bayer, and Lilly for Dr. Berger to perform consultant activities and to participate in steering committees for clinical trials. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Manuscript received August 5, 2015; revised manuscript received December 2, 2015, accepted January 5, 2016.

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Pulmonary arterial hypertension (PAH) is a severe disease in which pulmonary artery remodeling leads to an increase in pulmonary vascular resistance and pulmonary arterial pressure eventually resulting in right ventricular failure and death. Despite evolving treatment guidelines and the availability of PAH-targeted therapies, PAH prognosis remains very unfavorable in children (1-3).

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Pulmonary hypertension (PH)-specific treatment regimens can be divided into calcium-channel blockers (CCB) and PAH-targeted therapy. A small subset of idiopathic/familial PAH (IPAH/FPAH) patients have a sustained favorable outcome when treated with CCB, without the need for additional PAH-targeted therapy (1,4-6). It is therefore of utmost importance to identify patients who respond favorably to CCB therapy. According to both adult and pediatric treatment guidelines, acute vasodilator response testing (AVT) identifies these patients (7,8).

Currently, AVT is used for different purposes in patients with PAH: 1) selecting IPAH/FPAH-patients for CCB therapy; 2) assessing long-term prognosis; and 3) assessing defect operability in children with congenital heart disease (CHD) associated with PAH (8,9). It is important to note that the AVT criteria used for the first 2 purposes will be discussed in this article and that the proposed criteria are not designed nor appropriate for assessing operability in CHD.

Over time, different AVT criteria have been proposed to assess which patients should be treated with CCB (2,4,5,9-14). Eventually these criteria evolved into adult criteria proposed by Sitbon et al. that were adopted by the American College of Cardiology Foundation/American Heart Association (15) and European Society of Cardiology guidelines (7) on PH. For children with PAH, other criteria have been proposed, most recently modified by the REVEAL (Registry-to-Evaluate-Early-And-Long-term PAH disease management) registry investigators studying a subcohort of childhood-onset PAH patients (2,5,7).

Adult IPAH/FPAH patients with an acute response based on the Sitbon et al. (5) criteria have been shown to respond well to CCB therapy with sustained hemodynamic improvement and low World Health Organization functional class (WHO-FC). In contrast, less selective AVT criteria performed less well in identifying adult patients with a long-term CCB treatment response (5). For children with PAH, Yung et al. (6) showed that responders, according to the REVEAL-pediatric criteria, had favorable outcomes when treated with CCB, although long-term CCB treatment success rate was low and a way of predicting treatment success was not found. Furthermore, there is no generally accepted standard on how and with which agent to test acute vasodilator response in children. Therefore, more data on AVT and CCB therapy in pediatric PAH are needed.

The purpose of this study was to evaluate current clinical practice of AVT and subsequent treatment decisions in pediatric PAH in the international TOPP (Tracking-Outcomes-and-Practice-in-Pediatric-Pulmonary-Hypertension) registry (Online Appendix).

METHODS

A center-based registry initiated January 31, 2008, the TOPP registry covers 31 centers in 19 countries (16). The TOPP registry collects data on the assessment, treatment, and follow-up of pediatric PH patients. Participating centers include consecutive patients between 3 months and 18 years of age presenting with PAH or with PH groups 3 to 5 (classified according to the 2003 Third World Pulmonary Hypertension Symposium) and diagnosed on or after January 1, 2001 (16).

Patients were eligible for TOPP inclusion when meeting pre-specified hemodynamic criteria: mean pulmonary arterial pressure (mPAP) of ≥25 mm Hg, pulmonary vascular resistance index (PVRi) of ≥3 WU·m^2, and a mean pulmonary capillary wedge pressure of ≤12 mm Hg (17). Cardiac output was determined either by thermodilution in the absence of intra- or extra-cardiac shunts, or calculated by Fick method using either measured oxygen consumption provided by the treating physician or assumed oxygen consumption, according to LaFarge and Miettinen (18). Hemodynamic data of all included patients were reviewed by the TOPP registry executive board members to confirm diagnosis, leading to a cohort of right heart catheterization (RHC) confirmed PH patients (PH-confirmed).

For the current study, data from the May 2013 data export were analyzed and all PH-confirmed patients (n = 529) (**Figure 1**) were eligible for inclusion. Patients in whom no AVT was performed at diagnostic RHC or the administered vasodilator during AVT was considered inadequate (supplemental oxygen concentration FiO_2 <0.45) or unknown were excluded from the analyses, as were patients with incomplete pressure or flow data at AVT.

For all included patients, the treating physicians stated whether they considered the patient to be an acute responder or not. These data were compared to

ABBREVIATIONS AND ACRONYMS

AVT = acute vasodilator response testing

CCB = calcium-channel blocker

CHD = congenital heart disease

iNO = inhaled nitric oxide

IPAH/FPAH = idiopathic/familial pulmonary arterial hypertension

mPAP = mean pulmonary arterial pressure

mSAP = mean systemic arterial pressure

PAH = pulmonary arterial hypertension

PH = pulmonary hypertension

PVRi = pulmonary vascular resistance index

RHC = right heart catheterization

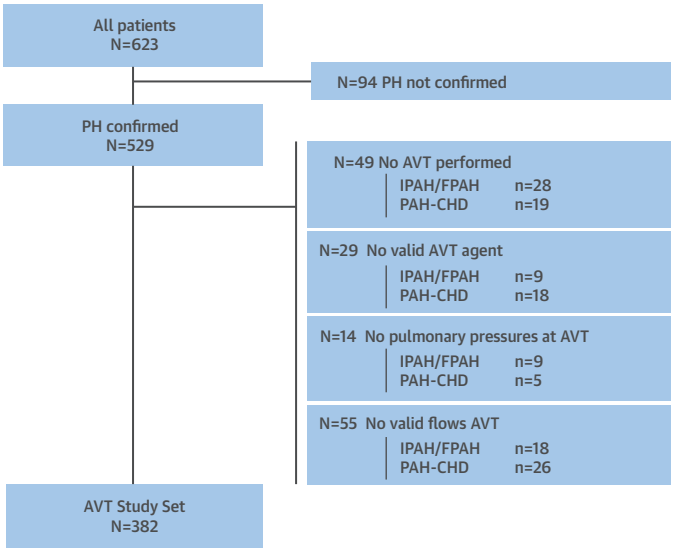
WHO-FC = World Health Organization functional class

acute vasodilator response at diagnosis, determined post hoc by re-evaluating the diagnostic hemodynamic data using the REVEAL-pediatric criteria proposed by Barst et al. (2) and the Sitbon criteria (5), adopted by the American College of Cardiology Foundation/American Heart Association (15) and European Society of Cardiology (7) PH guidelines (**Table 1**).

The proportion of AVT responders was analyzed for patients with IPAH/FPAH separately from patients in other diagnostic subgroups, because these acute response criteria were primarily designed for IPAH/FPAH patients and not validated for other diagnoses. For IPAH/FPAH patients, patient characteristics, hemodynamic profile, and initial treatment of AVT responders were compared to nonresponders. Treatment was classified as CCB with or without additional PAH-targeted therapy (CCB ± PAH-targeted therapy), PAH-targeted therapy (without CCB), or no PH-specific therapy. Also, for the IPAH/FPAH patients, patient characteristics, and hemodynamic profiles were compared between those who did or did not receive CCB.

STATISTICAL ANALYSES. Statistical comparisons were made using Student *t* test, Mann-Whitney *U* test, and chi-square test, as appropriate. Differences between the acute response at the discretion of the treating physician versus by criteria were tested using the McNemar test. Transplant-free survival was analyzed from diagnosis to death/lung transplantation or last follow-up visit using Kaplan-Meier curves and log-rank tests. Analyses were performed using SPSS 18.0 (IBM, Armonk, New York). The level of significance was defined as $p < 0.05$, 2-sided.

FIGURE 1 Patient Inclusion



After not including patients whose pulmonary hypertension (PH) could not be hemodynamically confirmed, patients in whom either no acute vasodilator response testing (AVT) was performed, the AVT agent was not adequate (unknown or low-dose oxygen), or data on either pressures or flow were not complete were excluded. IPAH/FPAH = idiopathic/familial pulmonary arterial hypertension; PAH-CHD = pulmonary arterial hypertension associated with congenital heart disease.

RESULTS

In May 2013, the TOPP registry included 529 pediatric patients with confirmed PH. We excluded 147 patients without complete AVT, which included 64 of 276 IPAH/FPAH patients (23%), leaving 382 patients included in the current study (**Figure 1**). Of these patients, 212 had IPAH/FPAH, 105 PAH-CHD, and 65 another form of PH (associated PAH excluding CHD, PH group 3, or PH group 4 to 5). In one-half of the children, heart catheterization was performed under general anesthesia; in the other one-half, procedural sedation was used. The majority (70%) of the included patients had AVT with inhaled nitric oxide (iNO) with or without additional O_2. The other patients were tested with various other agents (**Table 2** for numbers per diagnosis).

IPAH/FPAH PATIENTS. Of the IPAH/FPAH patients, 78 of 212 (37%) were considered acute responders by their treating physician. According to the REVEAL-pediatric criteria and the Sitbon criteria, these numbers were 62 (30%) and 32 (15%), respectively (**Central Illustration**). There was a notable discrepancy between the responder status assessed by the treating physician and that assessed by reported criteria (McNemar $p = 0.050$ and $p < 0.001$ for the REVEAL-pediatric and Sitbon criteria, respectively) (**Table 3**). Specifically, a high number of patients were regarded responders by their physicians, but not according to the criteria (29 for the REVEAL-pediatric criteria, 49 for the Sitbon criteria). Of the patients regarded as nonresponders by their physician, 15 were responders according to REVEAL-pediatric criteria and 3 per the Sitbon criteria.

All 32 Sitbon responders were also REVEAL-pediatric responders (**Table 3**). The remaining 30 REVEAL registry responders showed either a decrease of cardiac index ($n = 16$) at AVT or a >20% drop in mPAP that, however, remained >40 mm Hg ($n = 18$) or was <10 mm Hg ($n = 6$), which precluded acute responder status by Sitbon criteria. Of the 32 patients who reached a normal mPAP at AVT (<25 mm Hg, range 18 mm Hg to 24 mm Hg), 7 had a decrease of mPAP <10 mm Hg, precluding them from being a Sitbon responder.

TABLE 1 Acute Vasodilator Response Criteria

Physician's Judgment
• An acute response at the discretion of the treating physician
REVEAL-pediatric criteria by Barst et al. (2)
• A decrease in mPAP of ≥20% • And an unchanged, increased, or less than 10% decreased cardiac index • And a decreased or unchanged pulmonary-to-systemic vascular resistance ratio
Adult criteria by Sitbon et al. (5,7)
• Reduction of mPAP of ≥10 mm Hg • To reach an absolute value of mPAP ≤40 mm Hg • And an increased or unchanged cardiac output

mPAP = mean pulmonary arterial pressure; REVEAL = Registry to Evaluate Early And Long-term PAH disease management.

In IPAH/FPAH patients, acute responders according to the REVEAL-pediatric or Sitbon criteria were more often female than male than nonresponders. There were significantly more responders in the patients tested under procedural sedation compared to patients under general anesthesia. No differences in age, weight, height, body mass index, occurrence of (near-)syncope or WHO-FC were demonstrated between responders and nonresponders. The proportion of acute responders was not associated with age at diagnostic RHC. Acute responders compared to nonresponders (whether based on Sitbon criteria, REVEAL-pediatric criteria, or physician's judgment) had a more favorable hemodynamic profile, characterized by lower mPAP, mean right atrial pressure, PVRi, mPAP/mean systemic arterial pressure (mSAP), and pulmonary-to-systemic vascular resistance ratio both at baseline and at AVT, and a higher cardiac index at AVT (Table 4).

Acute responders were more often treated with CCB than nonresponders. However, of the 78 patients judged by their physician to be responders, only 18 (23%) were treated with CCB monotherapy and 11 (14%) received CCB with additional PAH-targeted therapy (Figure 2). Three of the responders not treated with CCB were <1 year of age and an additional 9 were in WHO-FC IV, which might explain why no CCB was initiated, leaving 37 patients (59%) not treated with CCB while they were >1 year of age, in WHO-FC I to III, and judged to be an acute responder. IPAH/FPAH patients who were prescribed CCB had a lower mPAP, mean right atrial pressure, PVRi, PVRi/systemic vascular resistance index and mPAP/mSAP, both at baseline and at AVT, and a higher cardiac index at AVT, compared to those who did not receive CCB (Table 5).

Median follow-up was 3.5 years (1.7 to 5.9 years). Acute responders, as judged by the treating physician, had a significantly better transplant-free

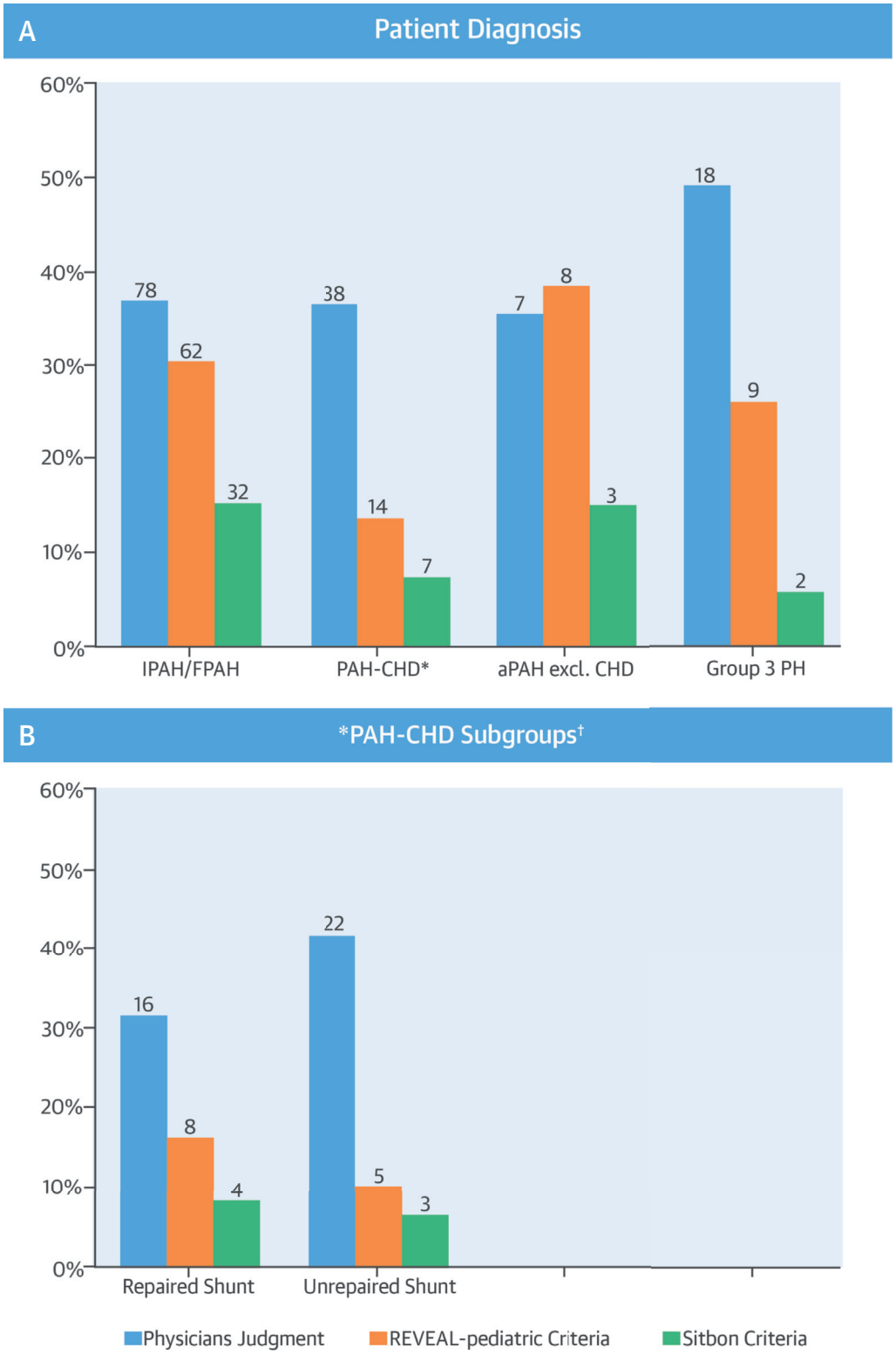
TABLE 2 Patient Characteristics

	Diagnostic Subgroup				
	IPAH/FPAH (n = 212)	PAH-CHD (n = 105)	aPAH excl. CHD (n = 21)	PH Group 3 (n = 38)	PH Groups 4 and 5 (n = 6)
Age at diagnosis, yrs	7.8 (4.2–13.0)	6.1 (2.3–11.9)	10.8 (7.2–14.1)	3.7 (1.4–9.7)	13.3 (6.1–13.6)
Female	133 (62.7)	60 (57.1)	11 (52.4)	23 (60.5)	2 (33.3)
Incident patients	106 (50)	54 (51.4)	10 (47.6)	17 (44.7)	4 (66.7)
WHO functional class					
I	28 (13.2)	15 (14.3)	3 (14.3)	6 (15.8)	1 (16.7)
II	89 (42.0)	52 (49.5)	8 (38.1)	19 (50.0)	2 (33.3)
III	73 (34.4)	37 (35.2)	6 (28.6)	12 (31.6)	3 (50.0)
IV	22 (10.4)	1 (1.0)	4 (19.0)	1 (2.6)	
Sedation method at HC					
General anesthesia	101 (47.9)	56 (53.8)	12 (57.1)	22 (57.9)	2 (33.3)
Procedural sedation	110 (52.1)	48 (46.2)	9 (42.9)	16 (42.1)	4 (66.7)
Baseline mPAP, mm Hg	59 ± 18	58 ± 20	50 ± 15	45 ± 15	60 ± 10
Baseline mRAP, mm Hg	7 ± 4	7 ± 4	7 ± 3	7 ± 3	8 ± 3
Baseline PVRi, WU·m^2	15.9 (10.5–22.6)	11.9 (8.1–20.3)	12.5 (8.6–18.3)	9.0 (6.4–11.5)	17.3 (13.2–24.0)
Baseline cardiac index, l/min/m^2	3.1 (2.4–4.1)	3.3 (2.5–3.9)	3.3 (3.0–4.0)	3.3 (2.8–4.6)	3.4 (1.8–4.1)
AVT agent					
iNO (and O_2)	152 (71.7)	64 (61.0)	15 (71.4)	32 (84.2)	3 (50.0)
Other*	60 (28.3)	41 (39.0)	6 (28.6)	6 (15.8)	3 (50.0)

Values are median (interquartile range), n (%), or mean ± SD. *Other agents included adenosine, diltiazem, epoprostenol, iloprost, oxygen, and sildenafil.

aPAH excl. CHD = associated pulmonary arterial hypertension excluding congenital heart disease; AVT = acute vasodilator response testing; HC = heart catheterization; IPAH/FPAH = idiopathic/familial pulmonary arterial hypertension; iNO = inhaled nitric oxide; mRAP = mean right atrial pressure; PAH-CHD = pulmonary arterial hypertension associated with congenital heart disease; PH = pulmonary hypertension; PVRi = pulmonary vascular resistance index; WHO = World Health Organization; WU = Woods units; other abbreviations as in Table 1.

CENTRAL ILLUSTRATION **Acute Vasodilator Response in Pediatric PAH: Number of Acute Responders**



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survival, compared to nonresponders (Figure 3A). In a second survival analysis (Figure 3B), the Sitbon responders (n = 32) were compared to the non-Sitbon REVEAL responders (n = 30) and the nonresponders. Sitbon responders had better transplant-free survival compared to all other IPAH/HPAH patients. In contrast, the transplant-free survival of the 30 REVEAL registry responders who were not Sitbon responders was comparable to that of the nonresponders.

In order to analyze the benefit of CCB in acute responders, we compared the survival of patients on CCB (whether in combination with [±] PAH-targeted therapy) with patients on PAH-targeted therapy (without CCB). Within the group of children judged to be responders by their physicians, no better transplant-free survival could be demonstrated in children treated with CCB compared to those receiving only PAH-targeted therapy (without CCB) (Figure 4A). In contrast, acute responders according to the Sitbon criteria treated with CCB ± PAH-targeted therapy (n = 20) had an excellent 100% survival, which seems better than acute responders on only PAH-targeted therapy (without CCB), although this difference did not reach statistical significance (Figure 4B). Also, Sitbon responders on CBB monotherapy (n = 15) had a 100% survival. Finally, REVEAL registry responders who were not Sitbon responders treated with CCB had comparable survival to those treated with only PAH-targeted therapy (without CCB) (Figure 4C).

NON-IPAH/FPAH PATIENTS. The response-criteria used here were neither designed nor appropriate for patients with other forms of PAH than IPAH/HPAH. Only for epidemiological comparison, we report the prevalence of acute responders in other forms of PH within the TOPP registry. Thirty-six percent of PAH-CHD patients were regarded by their physicians to be acute responders, which was comparable to the IPAH/FPAH group (37%). The percentages of responders according to the REVEAL-pediatric criteria (13%) and Sitbon criteria (7%) in PAH-CHD patients were significantly lower compared to pediatric IPAH/FPAH patients (p = 0.001 and p = 0.32, respectively). Within the PAH-CHD children, no statistically significant difference in percentage of acute responders could be demonstrated between those with repaired or unrepaired (including partially repaired) shunts (Central Illustration). The percentage of patients who were acute responders in the associated PAH excluding CHD group did not statistically differ from the IPAH/FPAH group for all 3 criteria (Central Illustration). In patients with PH due to respiratory disease, the percentages of responders according to the treating physician seemed larger, whereas the percentage of acute responder according to the REVEAL-pediatric and Sitbon criteria seemed lower compared to the pediatric IPAH/FPAH patients (Central Illustration). However, no statistically significant differences could be demonstrated in these last comparisons.

TABLE 3 Crosstab of Acute Vasodilator Response Criteria

		REVEAL-Pediatric Criteria		Sitbon Criteria	
IPAH/FPAH (n = 212)	**Responder**	**Yes**	**No**	**Yes**	**No**
Physician's judgment	Yes	47 (22.9)	29 (14.1)	29 (13.7)	49 (23.1)
	No	15 (7.3)	114 (55.6)	3 (1.4)	131 (61.8)
REVEAL-pediatric criteria	Yes			32 (15.6)	30 (14.6)
	No			–	143 (69.8)

Values are n (%).

IPAH/FPAH = idiopathic/familial pulmonary arterial hypertension; REVEAL = Registry to Evaluate Early And Long-term PAH disease management.

DISCUSSION

This study, using data from the worldwide TOPP registry, provided an overview of clinical practice of AVT in pediatric PH between 2001 and 2013. In the reported cohort, AVT was not performed or inadequately performed in 23% of children with IPAH/FPAH, although international treatment guidelines since 2009 dictate AVT in IPAH/FPAH patients to determine whether treatment with CCB therapy is warranted. Furthermore, there are substantial discrepancies between the presence of an acute response as judged by the treating physician versus assessed by reported AVT criteria. In clinical practice, a variety of vasodilating agents was used to perform AVT. We concluded that the reported pediatric clinical practice is not congruent with current diagnosis and treatment guidelines for PAH based on international consensus regarding the selection of patients in

CENTRAL ILLUSTRATION

Differences in acute vasodilator response testing are noted among **(A)** responders separated for the different criteria and diagnosis as well as **(B)** subgroups of patients with pulmonary arterial hypertension associated with congenital heart disease (PAH-CHD) with a repaired versus unrepaired (including partially repaired) shunt. aPAH excl. CHD = associated pulmonary arterial hypertension excluding congenital heart disease; IPAH/FPAH = idiopathic/familial pulmonary arterial hypertension; PH = pulmonary hypertension. *Refers to PAH-CHD subgroups. †PAH-CHD never shunt not included because n = 1.

TABLE 4 Characteristics of Acute Vasodilator Responders Versus Nonresponders

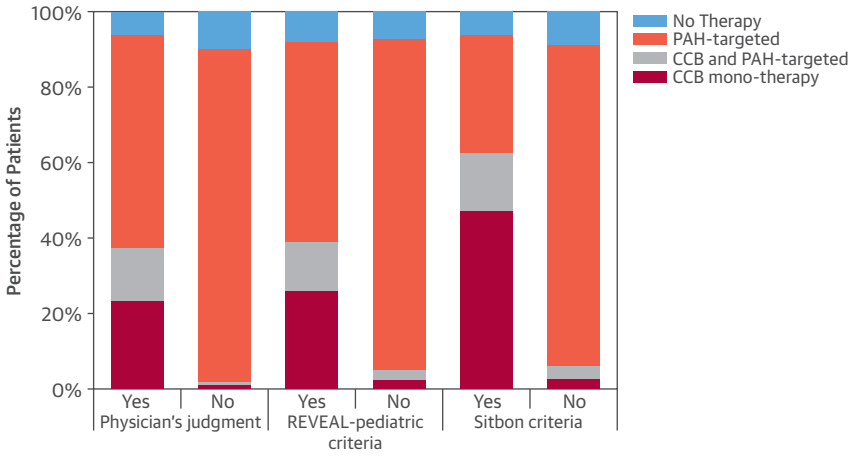
	Responder According to:								
	Physician's Judgment			REVEAL-Pediatric Criteria			Sitbon Criteria		
IPAH/FPAH (n = 212)	Yes	No	p Value	Yes	No	p Value	Yes	No	p Value
Age at diagnosis, yrs	7.1 (4.2–12.1)	8.1 (4.2–13.4)	0.187	7.3 (4.2–13.0)	8.0 (4.3–13.1)	0.789	8.5 (4.7–12.8)	7.4 (4.0–13.2)	0.731
Female	53 (67.9)	80 (59.7)	0.231	47 (75.8)	81 (56.6)	0.009	28 (87.5)	105 (58.3)	0.002
Incident patients	33 (42.3)	73 (54.5)	0.087	35 (56.5)	67 (46.9)	0.207	17 (53.1)	89 (49.4)	0.701
WHO functional class									
I	13 (16.7)	15 (11.2)	0.314	7 (11.3)	20 (14.0)	0.407	2 (6.3)	26 (14.4)	0.620
II	36 (46.2)	53 (39.6)		27 (43.5)	58 (40.6)		17 (53.1)	72 (40.0)	
III	16 (20.5)	57 (42.5)		16 (25.8)	55 (38.5)		7 (21.9)	66 (36.7)	
IV	13 (16.7)	9 (6.7)		12 (19.4)	10 (7.0)		6 (18.8)	16 (8.9)	
Sedation method at HC									
General anesthesia	29 (28.7)	72 (71.3)	0.017	23 (24.2)	72 (75.8)	0.097	8 (7.9)	93 (92.1)	0.005
Procedural sedation	49 (44.5)	61 (55.5)		38 (34.9)	71 (65.1)		24 (21.8)	86 (78.2)	
Baseline mPAP, mm Hg	56 ± 16	62 ± 19	0.018	54 ± 16	62 ± 19	0.002	49 ± 13	61 ± 18	<0.001
AVT mPAP, mm Hg	37 ± 17	56 ± 19	<0.001	33 ± 12	56 ± 19	<0.001	27 ± 8	53 ± 19	<0.001
Baseline mRAP, mm Hg	6 ± 3	8 ± 4	0.001	6 ± 4	7 ± 4	0.002	5 ± 3	7 ± 4	<0.001
AVT mRAP, mm Hg	6 ± 3	8 ± 4	0.002	6 ± 3	8 ± 4	<0.001	5 ± 3	7 ± 4	<0.001
Baseline PVRi, WU·m^2	13.5 (8.6–19.5)	17.3 (11.3–24.2)	0.007	12.7 (7.9–18.9)	16.7 (12.1–24.2)	0.002	12.9 (8.0–18.5)	16.3 (10.9–23.9)	0.006
AVT PVRi	6.0 (4.0–10.6)	15.2 (8.7–22.4)	<0.001	4.5 (3.6–9.1)	14.8 (8.7–22.3)	<0.001	4.2 (3.1–5.9)	12.6 (7.4–20.0)	<0.001
Baseline cardiac index, l/min/m^2	3.3 (2.8–4.3)	2.9 (2.2–3.8)	0.018	3.2 (2.7–4.4)	2.9 (2.4–4.0)	0.082	3.2 (2.8–4.4)	3.0 (2.4–4.0)	0.251
AVT cardiac index, l/min/m^2	3.6 (2.9–4.5)	3.1 (2.3–4.1)	0.003	3.8 (3.0–5.0)	3.1 (2.3–3.9)	<0.001	4.2 (3.4–5.1)	3.1 (2.4–4.0)	<0.001
Baseline PVRi/SVRi	0.8 (0.6–0.9)	0.9 (0.7–1.2)	0.004	0.7 (0.5–0.9)	0.9 (0.7–1.1)	0.001	0.7 (0.5–0.8)	0.9 (0.7–1.1)	<0.001
AVT PVRi/SVRi	0.4 (0.2–0.6)	0.7 (0.5–1.0)	<0.001	0.4 (0.2–0.5)	0.7 (0.5–1.0)	<0.001	0.3 (0.2–0.4)	0.7 (0.4–1.0)	<0.001
Baseline mPAP/mSAP	0.8 (0.6–1.0)	0.9 (0.7–1.1)	0.007	0.8 (0.6–1.0)	0.9 (0.7–1.1)	0.004	0.7 (0.6–0.9)	0.9 (0.7–1.1)	<0.001
AVT mPAP/mSAP	0.5 (0.3–0.7)	0.8 (0.6–1.0)	<0.001	0.4 (0.3–0.6)	0.8 (0.6–1.0)	<0.001	0.4 (0.3–0.5)	0.7 (0.5–1.0)	<0.001
AVT agent									
iNO (and O_2)	50 (64.1)	102 (76.1)	0.061	47 (75.8)	102 (71.3)	0.509	23 (71.9)	129 (71.7)	0.981
Other	28 (35.9)	32 (23.9)		15 (24.2)	41 (28.7)		9 (28.1)	51 (28.3)	

Values are median (interquartile range), n (%), or mean ± SD.
mSAP = mean systemic arterial pressure; SVRi = systemic vascular resistance index; other abbreviations as in Tables 1 and 2.

whom to perform an AVT, the agent to use for this test, and the criteria used to determine the response (7,8). There is a need for improvement and consistency. The data of our current study may help to achieve evidence-based recommendations (8).

Compared to the REVEAL-pediatric criteria, the Sitbon criteria are the more selective. It has been insufficiently clear whether the use of more selective criteria in pediatric patients would lead either to a more accurate selection of children who will benefit from CCB therapy and a better prognostic value or to an unjustified exclusion of children who would be identified with less strict criteria and who might also benefit from CCB therapy. In the current study, we distinguished 3 groups of patients: 1) Sitbon responders (all of whom also appeared to be REVEAL registry responders); 2) REVEAL registry responders who were not Sitbon responders; and 3) nonresponders for both criteria. Transplant-free survival of Sitbon responders was superior compared to Sitbon nonresponders. Furthermore, children with IPAH/FPAH who were Sitbon responders had excellent transplant-free survival when initially treated with CCB. In contrast, acute responders according to the less strict REVEAL-pediatric criteria, who had not met the Sitbon criteria, had a transplant-free survival similar to that of nonresponders. Of these REVEAL registry responders not fulfilling Sitbon criteria, the children treated with CCB, whether in combination with PAH-targeted therapy, had comparable outcomes to those treated with only PAH-targeted therapy. These data strongly suggest superiority of the Sitbon criteria over the REVEAL-pediatric criteria in identifying pediatric patients with improved survival who will benefit from CCB therapy. Whereas children identified by only REVEAL-pediatric criteria seem to have no better outcome compared to nonresponders and no benefit from CCB therapy. A previous study by Yung et al. indeed showed that the success rate of long-term CCB therapy was relatively low in children with IPAH/FPAH selected with the less strict REVEAL-pediatric criteria (6). This followed data from adult PAH patients that showed the Sitbon criteria were superior to

FIGURE 2 Treatment of Acute Vasodilator Responders



Initial treatment of acute vasodilator responders versus nonresponders in pediatric IPAH/FPAH patients varied depending on the acute vasodilator response criteria. CCB = calcium-channel blocker; other abbreviations as in Figure 1.

less strict criteria in selecting patients who will have a sustained response to CCB therapy (5). In summary, the current data suggest that the use of Sitbon criteria is preferred, not only in adults but also in children with IPAH/FPAH, when selecting patients for CCB therapy.

It has been questioned whether the Sitbon criteria, with its required absolute pulmonary arterial pressure reduction, are applicable in young children. According to current guidelines, the definition of PH is independent of age and requires an absolute mPAP value >25 mm Hg (8). Infants may have relatively lower values of baseline mPAP and may reach normal mPAP values (<25 mm Hg) during AVT but without an absolute decrease of 10 mm Hg. The current data showed that this occurred in 7 of 212 IPAH/FPAH patients (3%). The prognosis of this small subgroup of patients is indeed insufficiently defined. However, the small number of children in whom this applies does not preclude using the Sitbon criteria in pediatric PAH.

Interestingly, acute response to AVT by the treating physician's judgment seemed to perform well in differentiating patients with better versus worse outcome. This might be explained by the physician involving additional clinical parameters to judge a patient's responder status and make treatment choices. In the current study, this is supported by the observation that physician-identified responders had a more favorable baseline hemodynamic profile. Therefore, acute response, as judged by the treating physician using a broad array of clinical data, may be

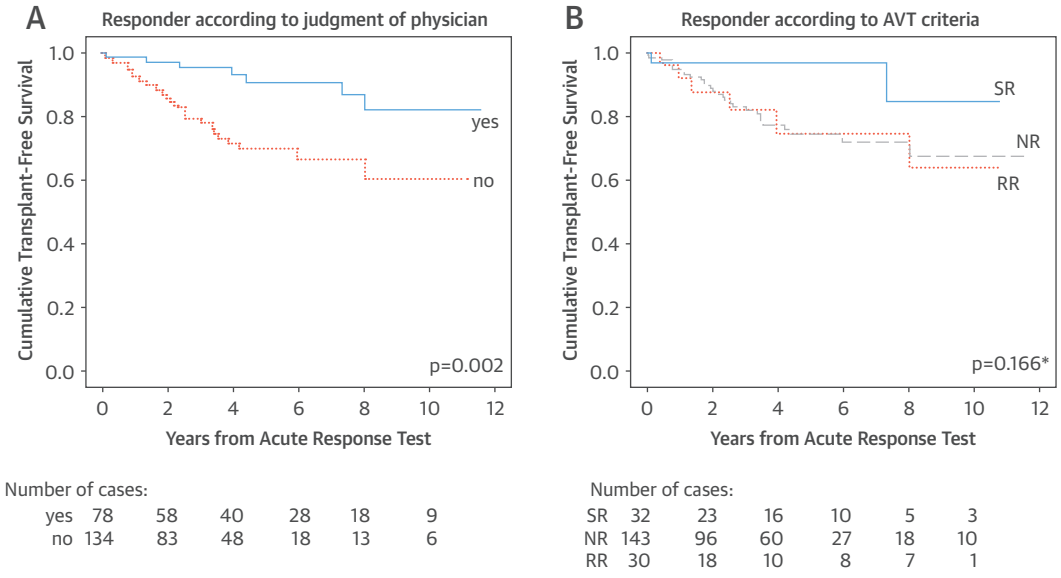
TABLE 5 Patient Characteristics Stratified for Therapy

IPAH/FPAH (n = 212)	CCB ± PAH-Targeted (n = 31)	PAH-Targeted (n = 163)	No Therapy (n = 18)	p Value*
Age at diagnosis, yrs	7.3 (4.6-12.9)	8.0 (3.9-13.2)	6.0 (4.2-13.1)	0.833
Female	26 (83.9)	94 (57.7)	13 (72.2)	0.008
Incident patients	14 (45.2)	82 (50.3)	10 (55.6)	0.560
WHO functional class				
I	3 (9.7)	19 (11.7)	6 (33.3)	0.280
II	18 (58.1)	67 (41.1)	4 (22.2)	
III	7 (22.6)	59 (36.2)	7 (38.9)	
IV	3 (9.7)	18 (11.0)	1 (5.6)	
WHO functional class				
I and II	21 (67.7)	86 (52.8)	10 (55.6)	0.128
III and IV	10 (32.3)	77 (47.2)	8 (44.4)	
6-min walking distance, min	414 ± 128	397 ± 127	358 ± 104	0.557
Baseline mPAP, mm Hg	50 ± 16	61 ± 18	62 ± 18	0.002
Baseline mRAP, mm Hg	5 ± 3	7 ± 4	8 ± 4	<0.001
Baseline PVRi, WU·m^2	13.0 (7.4-18.6)	15.9 (10.9-22.9)	21.3 (8.0-26.5)	0.014
Baseline cardiac index, l/min/m^2	3.3 (2.9-4.3)	2.9 (2.4-4.0)	3.0 (2.0-4.0)	0.133
Baseline PVRi/SVRi	0.6 (0.4-0.8)	0.9 (0.7-1.1)	0.8 (0.7-1.1)	<0.001
Baseline mPAP/mSAP	0.7 (0.5-0.8)	0.9 (0.7-1.1)	0.9 (0.7-1.1)	<0.001
AVT mPAP, mm Hg	29 ± 14	52 ± 19	53 ± 20	<0.001
AVT mRAP, mm Hg	5 ± 4	7 ± 4	8 ± 3	0.003
AVT PVRi, WU·m^2	4.1 (3.2-5.9)	12.4 (7.0-19.7)	13.6 (8.2-22.9)	<0.001
AVT cardiac index, l/min/m^2	4.1 (3.4-5.1)	3.1 (2.4-4.1)	3.1 (2.4-4.1)	<0.001
AVT PVRi/SVRi	0.3 (0.2-0.4)	0.7 (0.4-1.0)	0.6 (0.4-0.9)	<0.001
AVT mPAP/mSAP	0.3 (0.3-0.5)	0.7 (0.5-1.0)	0.8 (0.5-1.1)	<0.001

Values are median (interquartile range), n (%), or mean ± SD. *The p value of patients on CCB ± PAH-targeted therapy (the CCB monotherapy group combined with the CCB and PAH-targeted therapy group) versus the other patients.

CCB = calcium-channel blocker; other abbreviations as in Tables 1, 2, and 4.

FIGURE 3 Survival Stratified for AVT Response Status



Patient survival was stratified for acute response status according to **(A)** physician's judgment of responders (yes) versus nonresponders (no), and **(B)** the different acute vasodilator response testing (AVT) criteria: Sitbon responders (SR); REVEAL (Registry-to-Evaluate-Early-And-Long-term PAH disease management) registry responders who were not Sitbon responders (RR); and nonresponders according to both criteria (NR). *Comparison of SR versus all other patients (RR and NR): $p = 0.058$.

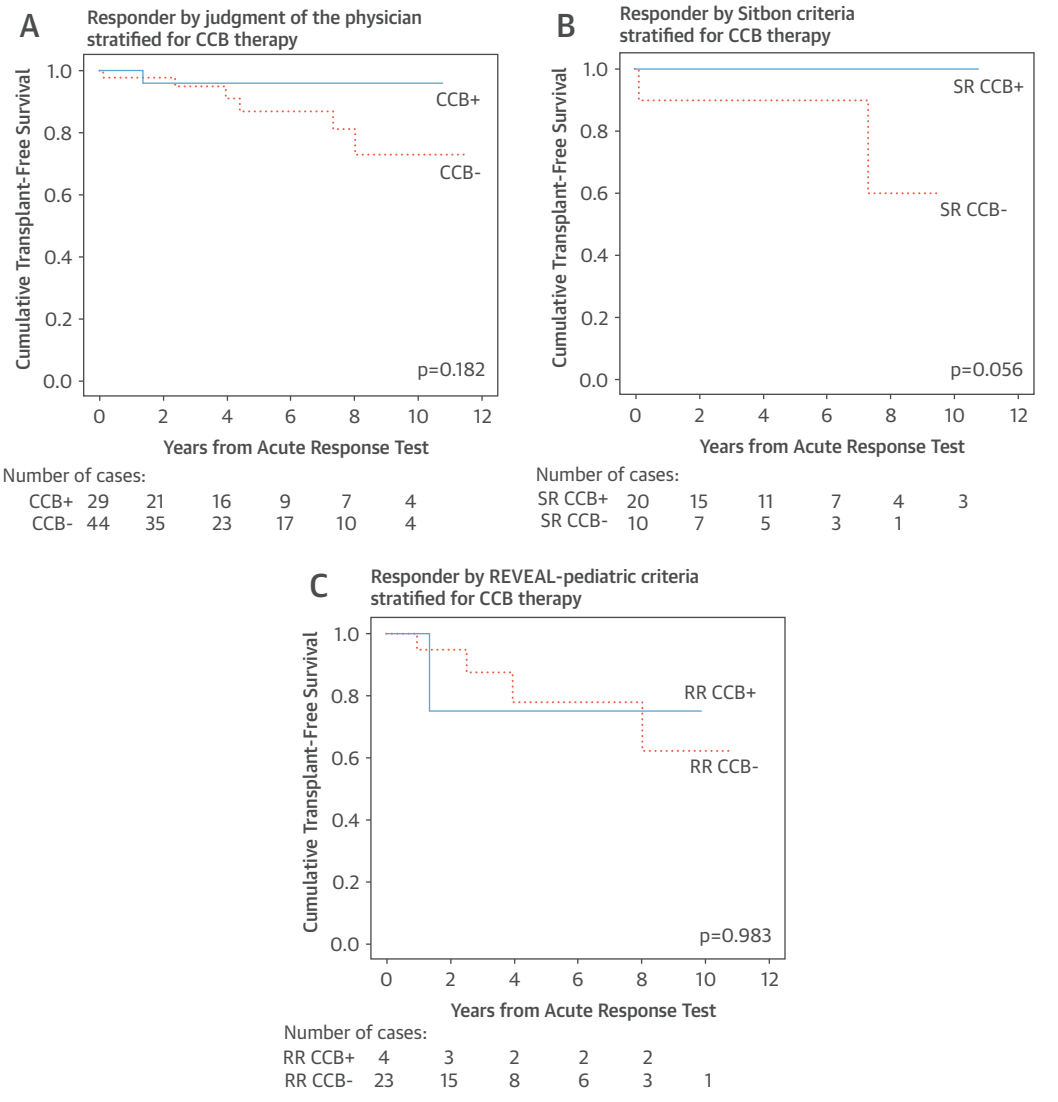
associated with favorable prognosis. However, physician's judgment did not perform as well as the Sitbon criteria in identifying patients who benefited from CCB therapy.

It has been postulated previously that children more often exhibit an AVT response than adult patients with IPAH/FPAH, possibly due to younger age (11,19). However, different criteria for acute responders that have historically been used in children and adult patients might have contributed to this assumed difference between pediatric and adult PAH (9). The AVT criteria, proposed for children with IPAH/FPAH, have gradually changed over time, leading to a range in reported percentages of responders in pediatric IPAH/FPAH from 13% to 56% (2,4,6,9,11). Using the REVEAL-pediatric criteria, we found that 30% of children with IPAH/FPAH qualified as acute responders. However, using the Sitbon criteria, only one-half of these children qualified as acute responders, which is comparable to percentages reported in adults with IPAH/FPAH using these same criteria (5% to 17%) (1,2,5,9,20,21). Moreover, in the current cohort, we could not demonstrate a correlation between age and acute responder status. The current data therefore confirmed the hypothesis that reported differences between children and adults in the proportion of acute responders can be attributed to historic use of less strict AVT criteria in the pediatric group, instead of a previously suggested correlation between age and the presence of an acute response in children (9).

In most patients in this study, iNO with or without additional O_2 was used to perform AVT. Available data suggest that nitric oxide is a potent, safe, and short-acting acute vasodilating agent in this setting. Combining iNO with oxygen seems even more potent (22–26). Other agents, such as iloprost and treprostinil, may be equally potent (24–26). Comparative data regarding the best agent or combination of agents to identify not only an acute response but those patients who respond well to long-term CCB therapy is lacking. Nevertheless, use of iNO is currently recommended in the guidelines for adult patients with PAH; it is the most frequently used agent and has been proven potent and safe in children, too (7,8). Therefore, we also recommend iNO as the agent of choice, if available, to perform AVT in pediatric PAH. The value of additional pulmonary vasodilator response to other or multiple agents for AVT remains to be elucidated (27).

The current study revealed that patients undergoing heart catheterization under procedural sedation

FIGURE 4 Survival of AVT Responders Stratified by CCB Therapy



Acute responders determined by **(A)** physician's judgment, **(B)** Sitbon criteria (SR), or **(C)** REVEAL (Registry-to-Evaluate-Early-And-Long-term PAH disease management)-pediatric criteria (RR). Only Sitbon Responders tended to survive longer over time when on CCB therapy PAH-targeted therapy (CCB+) versus only PAH-targeted therapy without CCB (CCB−). Abbreviations as in Figures 1 to 3.

more often showed an acute response than patients under general anesthesia. It is speculative whether this might be related to pulmonary vasodilating properties of certain anesthetic agents or to the maintenance of sympathetic activation during procedural sedation. This finding requires further investigation because they may directly affect the definition and interpretation of acute response in pediatric PAH.

In patients with IPAH/FPAH, current treatment guidelines propose to initiate treatment with CCB when acute response can be achieved and the patient is not in WHO-FC IV, whereas PAH-targeted therapy is advised when an acute response cannot be achieved. However, in the studied pediatric cohort, the majority of patients considered acute responders by their treating physician were not treated with CCB therapy. Currently it is advised not to treat children <1 year of age with CCB because of potential negative inotropic effects (8), which may also disincline physicians from treating patients with right ventricular failure or in high WHO-FC (IV) with CCB, as proposed by the adult treatment algorithm for

PAH (7). In our study, however, these considerations insufficiently explained the large number of patients considered acute responders by their physician left untreated with CCB therapy.

Compared to those who did not receive CCBs, patients treated with CCB therapy appeared to have a better baseline hemodynamic profile, a factor that may have affected the decision to use CCB therapy. This treatment decision, however, did not adhere to current treatment guidelines. Children who show an acute response at AVT have a favorable outcome when treated with CCB; therefore, withholding this treatment may not be in their best interest (1).

The percentage of AVT responders differed in patients with other types of PAH than IPAH/FPAH. PAH-CHD patients showed a lower percentage of acute responders, regardless of the presence of a repaired or unrepaired shunt. It is important to note that the described AVT criteria were designed specifically to identify IPAH/FPAH patients who will benefit from CCB therapy and explicitly not for patients with other forms of PAH. Both the Sitbon and REVEAL-pediatric criteria require a significant drop in mPAP. It should be emphasized that in patients with a nonrestrictive shunt defect at post-tricuspid level, the mPAP equals mSAP and therefore mPAP can only decrease substantially when the systemic arterial pressure drops as well. Thus mPAP at AVT will not represent a pulmonary vasodilator response, precluding the use of the AVT criteria described in this report. It should further be emphasized that AVT is also used to assess reversibility of PAH-CHD and operability of congenital heart defects (28); however, the criteria discussed in the current manuscript are not suitable for this purpose.

STUDY LIMITATIONS. The TOPP registry is a prospective observational international disease registry with associated limitations. Because of the registry's observational nature, no standardized AVT protocol was prescribed nor the use of predefined response criteria or treatment strategies. Baseline hemodynamic measurements and AVT tests were performed using different protocols, including variation in baseline conditions and used acute vasodilator agents. The data did not allow us to investigate whether patients would have a more pronounced acute response with other or additional vasodilating agents. Only CCB therapy at diagnosis could be analyzed; no data were available on the course of treatment after initiation. Furthermore, not all acute responders were treated with CCB, prohibiting more definitive statements on which criteria perform best in selecting patients who will respond well to CCB. However, with its large sample size from a real-world population and its global generalizability, the TOPP registry is unique in providing important insights on current practice of AVT, subsequent treatment decisions, and outcome in children with PAH.

CONCLUSIONS

The proportion of acute pulmonary vasodilator responders in children with IPAH/FPAH, using the Sitbon criteria for acute response, was similar to that reported in adults with IPAH/FPAH and appeared unrelated to age. From a registry evaluating AVT in children with IPAH/FPAH from 2001 to 2013, the practice of identifying acute responders to AVT in children with IPAH/FPAH was widely variant and inconsistent with current internationally recommended diagnostic algorithms for both adult and pediatric patients. Furthermore, in reported clinical practice, the majority of children with IPAH/FPAH, classified as acute responders, were not treated with CCB therapy. The current study suggested that, as in adult IPAH/FPAH, the Sitbon criteria are the criteria of choice in pediatric IPAH/FPAH to identify children who will show sustained benefit from CCB therapy. It is advised to closely monitor acute responders treated with CCB therapy during follow-up so that initiation of PAH-targeted therapy is not delayed in case of CCB treatment failure.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE 1: The proportion of children with IPAH/FPAH who respond to AVT is similar to that in adult IPAH/FPAH patients.

COMPETENCY IN MEDICAL KNOWLEDGE 2: For children with IPAH/FPAH, the Sitbon criteria are the criteria of choice to identify acute vasodilator responders who show a sustained beneficial response to CCB therapy.

TRANSLATIONAL OUTLOOK: Further implementing current recommendations for AVT in pediatric pulmonary hypertension centers will help improve the selection of patients who will benefit from CCB therapy, which will improve patient outcome.

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KEY WORDS calcium-channel blocker therapy, congenital heart disease, mean arterial pressure, right heart catheterization

APPENDIX For a list of the TOPP Registry investigators, please see the online version of this article.